Naval Health Research Center

LIMITS OF TOLERANCE TO HYPOTHERMIA

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Report No. 93-15

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BETHESDA, MARYLAND

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Report number 93-15, supported by the Naval Medical Research and Development Command, Office of Naval Technology, Department of the Navy.

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INTRODUCTION:

Humans are able to withstand and recover from various degrees of low central temperatures (hypothermia). The following two clinical cases, that are separated by 225 years, substantiate the tolerance of the human body to a significant reduction in core temperature in which either a profound suppression or cessation of vital signs has been followed by complete recovery.

Case Report - 1756

In the year 1756, district medical officer Samuel Nauclér from the island of Gotland presented a paper in the Royal Swedish Academy of Sciences titled, "Report about a man, which from the appearance seemed frozen to death, but was escaped with his life!"

He reported that on March 24th the same year a sixty year old drunken sailor was found lifeless on a rock the day after his ship had wrecked. He appeared dead and was carried into a small cottage. His legs and arms were frozen hard and white. His joints were stiff and the jaws were locked. His eyes were open and did not react when I touched them. There were no palpable pulse. Nor heart sounds, neither breathing could be recorded. However, as his heart-pit was still somewhat warm, I decided to restore his circulation---. I rubbed his arms and legs with woolen rags. I covered his chest and abdomen with pieces of wet cloths, which I continuously warmed. Gradually his chest and abdomen became warmer. After four hours I observed some breathing and two hours later I felt a weak pulse and a little later I managed to prize up his mouth with the help of a teaspoon. I warmed some wine and added 20 drops of Gratia probatum and poured it down his throat. Suddenly he roared as an ox, and those standing around said he gave up the ghost. However, after a while he began to perspire in his face and his cheeks turned red.

Three hours later he started to blink and move his arms. Ten hours after starting my treatment, the sailor began mumbling. His legs were still white and cold. I put them into cold water and bandaged them. He ate an egg, drank a beer, and slept during the whole night. The following morning his feet were warm with normal colour but very tender. He complained of an intensive thirst. The next day he was taken by boat to his home where he praised me for saving him from eternal misfortune (35).

Case Report - 1981

A 41-year-old civil servant was buried by an avalanche and remained trapped under several feet of packed snow for 2 1/2 hours. When rescue came the patient stopped breathing and lapsed into cardiac arrest. After tracheal intubation on the scene by a doctor accompanying the Heliswiss aircraft, he was immediately flown to our emergency center in Berne. Cardiac massage was continued in the helicopter. Upon arrival we recorded ventricular fibrillation, a core temperature of 22°C measured rectally, and dilated fixed pupils. When all attempts at closed chest defibrillation had proved unsuccessful, thoracotomy was performed, and active rewarming started by continuous irrigation of the pericardial cavity and the stomach with warm saline. It took about 1 1/2 hours and 40 liters of saline to bathe the heart and raise the core temperature to 26°C, at which time the heart was defibrillated successfully. Strikingly, at the beginning of active rewarming, the heart was found to be hard as stone and it is hardly conceivable how effective external cardiac massage could have been during the helicopter flight. Apart from temporary pulmonary edema, the postoperative course was uneventful, and the patient was dismissed two weeks later with an astonishing full recovery of his intellectual and physical abilities (4).

DEFINING LIMITS OF HYPOTHERMIC TOLERANCE

The ability of the thermoregulatory system to maintain central body temperature within very narrow limits allows humans to have normal function in a broad range of environmental conditions. This volume is a testament to the efficacy of physiological systems to withstand extreme environmental conditions in acute and chronic situations. However, there are functional limits to the thermoregulatory system beyond which the survival of the individual becomes jeopardized and from which recovery may not be total or possible. This chapter will address the physiological consequences that ensue when core temperature continues to decrease due to the inability of physiological and behavioral mechanisms to reverse this downward trend. In addition, this chapter will consider hypothermic tolerance to involve the effectiveness of rewarming to reverse the consequences of a reduction in core temperature. This definition of human tolerance is different from that proposed by Adolph and Molnar (3) in which they evaluated metabolic rate, environmental temperature, and clothing insulation, to derive time-limits during which a person could function before hypothermia began. Since that initial study, rewarming is routinely used in reversing the hypothermic state, and in increasing a person's chances of recovery

from an otherwise fatal condition. The concept of tolerance to the cold, as presented by Adolph and Molnar (3), has been modified to include the reversibility by rewarming of cold-induced respiratory and circulatory arrest.

This chapter will emphasize human studies concerning the mechanisms of tolerance to hypothermia, but will utilize select animal studies which provide important insights. As discussed later in this chapter, there are various kinds of hypothermia due to both the variability of situations inducing it as well as to the physiological status of the hypothermic person. Furthermore, the majority of hypothermic incidents usually include an alteration in homeostatic mechanisms due either to drugs and/or to underlying pathology. In a nationwide study that reviewed the efficacy of various rewarming techniques, only one hypothermic person out of 428 had neither underlying pathology nor any detectable levels of drugs or medications (24).

Hypothermia is commonly defined as a 2°C decrease in central or "core" temperature (i.e., those of the vital organs: brain, spinal core, heart, lungs) from the normal 37°C value. This value (35°C) is considered the initial level of hypothermia; however, individuals who have had a core temperature as low as 16°C resulting from exposure to environmental cold or as low as 9°C, induced clinically, have been successfully rewarmed with no apparent long-term disability (25). Certain body temperature ranges have been used to categorize the physiological limits humans can tolerate and the potential for recovery with and without external intervention (Table 1).

Hypothermia can be categorized as primary, secondary, or clinically induced (iatrogenic). Primary refers to the condition of a decreased core temperature induced by environmental conditions that overwhelm normal physiological systems. Secondary hypothermia refers to a condition in which some alteration of function occurs in a number of physiological systems that control thermoregulation. Consequently, normal thermoregulatory function is impaired and subsequent cold environmental challenges will produce an ineffective thermal response resulting in a reduction in core temperature. Clinically induced hypothermia is a state

of decreased core temperature that is induced in preparation for certain surgical procedures and clinical protocols (e.g., the use of cardioplegic solutions).

It should be noted that these definitions are general and their associated symptoms, severity, and degree of reversibility (tolerance) will be influenced by a multitude of factors, such as the rate of cooling and/or the presence of various pharmacological substances. Additional classifications of hypothermia have been developed depending on those environmental conditions or physiological states which influence the depth and rate of onset of hypothermia (Table 2).

Hypothermia is usually associated with other physiological challenges (Table 2). Due to the inherent difficulty of interpretation of the data, limited studies have considered the interaction of multiple physiological stressors, including sleep deprivation, dehydration, hypoglycemia, mental status, fatigue, and decreased core temperature. As a consequence, many studies of hypothermia do not investigate the effect of these multiple stressors which normally accompany or precede hypothermia. Studies have been conducted in laboratory or field settings in which subjects had prolonged exposure to the cold ranging from 11 days to 3.5 weeks (60,29). A recent study by Opstad and Bahr (95) reflecting real-life scenarios, studied 15 male cadets involved in a six-day training course. The subjects were involved in around-the-clock activities corresponding to 35% of $\dot{V}O_2$ maximum and were placed on a semi-starvation diet. No organized sleep was allowed but they were able to sleep a total of 1 to 3 hours during the course of the exercise. Overall, the data demonstrated decreases in core temperatures with increases in peripheral temperatures and a 14% to 24% increase in $\dot{V}O_2$. The authors concluded that an alteration in set point might be induced by all of the combined stressors. This experiment, although realistic, allowed the subjects to drink water ad libitum and was conducted while the environmental temperature was mild (15°C to 20°C). Even in this study, there was no hypothermia since the rectal temperature fell to only 36.5°C. The converse of this study was one in which there was control for proper clothing, nutrition, and sleep in military subjects undergoing nine-day training field exercises. As expected, Hodgdon et al. (49) reported that there was no decrement in physical

or cognitive performance under these conditions. However, in most situations in which hypothermia occurs, adequate clothing, nutrition, and sleep are the exception and not the rule. Variations of tolerance to hypothermia are also determined by inherent physiological status, such as the age of the subject, the person's previous exposure to the cold. For example, newborns do not shiver as readily as adults because of the higher amounts of brown fat. Overall mental attitude is another variable that normally defies quantification. Depending on the situation, mental attitude can greatly change a person's limits of survivability.

HYPOTHERMIA-INDUCED PHYSIOLOGICAL CASCADE: LIMITS OF TOLERANCE

With so many associated external and internal interacting variables to influence tolerance limits, the approach that is utilized in this chapter is to consider each physiological system separately.

Utilizing knowledge of the response of the isolated organ or organ system to hypothermia, the sequential physiological phenomena that occurs during hypothermia are presented (Table 3).

A unifying theme for the effect of decrease in core temperature on a physiological system considers the suppressive effects of cold on the cellular metabolism of the system in question. Initially, in many environmental situations, cold can induce activation and then suppression of a physiological system by influencing the neural, endocrine, and oxygen delivery systems to that organ. Eventually the individual function of the cells composing the organ system in question is decreased. Although there are many ways for hypothermia to originate, the final result is its effect on the cell membranes and basic cellular metabolism. For example, in submersion hypothermia in which the person is simultaneously immersed and aspirates cold water, the victims are rapidly cooled both internally and externally. In secondary hypothermia, heat generating systems are impaired so that adequate thermogenesis is compromised, but the cooling rate is much slower and insidious than in submersion hypothermia. However, in both situations, the neurons of the central nervous system and the myocardial cells of the heart are compromised. The situation is complicated by

the presence of drugs (e.g., ethanol), which influences cellular response to a cold and thus limits tolerance. In general, during hypothermia, all physiological systems become depressed, but at significantly different rates. The explanation for this phenomenon is twofold: 1) the phenomenon of nonuniform cooling leads to relative hot and cold areas even within the various organs, and 2) the metabolic demand of various organs can vary in response to the thermal stress. Most physiological systems utilize both high and low energy demanding processes. With reduced temperature, low energy requiring functions, such as diffusion (ions, metabolites, and water) are sustained to a higher degree than energy, (e.g., adenosine triphosphate [ATP]) dependent processes such as phosphorylation (45). The concept of Q10 has been used to describe the effect of a 10°C rise on reaction rates. Although some chemical reactions change in a linear fashion, most have logarithmic change relative to a 10°C change. Change in temperature not only induces change in rate of chemical reactions but the resultant of these altered reactions is a change in the cellular pH. Cellular pH changes will also influence the chemical reaction rates (105). However, in addition to the effect of temperature on chemical reactions, cold also alters the lipoprotein matrix of the cell. Hence, as the cooling progresses, the membrane liquids undergo a phase transition from a fluid to a gel state (34).

Comparative studies conducted between hibernators and nonhibernators in hypoxic states have given insight into the mechanism(s) of hypothermia at the cellular level. Hypothermia has less of an effect on cells from hibernating animals since those cells are able to maintain near-normal membrane function in hypoxic conditions. Membrane function is defined as maintenance of a difference in normal ion concentration between various internal and external compartments in spite of greatly reduced cellular metabolic rates (48). In ischemic cells in nonhibernating animals, hypothermia assists in prolonging cellular function by making the membrane more rigid and minimizing fluxes similar to that occurring normally in hibernating animals. It has been suggested that the overall effect of hypothermia is to minimize the leakiness of cell membranes (decrease fluidity) that might be disrupted due to ischemia. This cold-induced reduction in

leakiness extends normal cellular function in hypoxic states and plays a key role in increasing the tolerance of cells to hypoxia.

CENTRAL NERVOUS SYSTEM

Some of the first clinical signs of hypothermia are alternations in higher functioning, such as slurring of speech, decreased consciousness, and impairment of short-term memory. As early as 1931, local brain cooling induced abnormal expression of function for the area cooled without the patient even acknowledging the deficit. In one study, local cooling of the inferior parietal lobe in a patient caused the patient to believe that his speech was being uttered by a stranger (12).

As core temperature decreases, neuronal and vascular changes occur that influence tolerance to hypothermia. Most individuals lose consciousness at a body temperature of 28°C to 30°C, but there are isolated cases of consciousness, as well as the ability to speak, when temperatures reached as low as 24°C (120).

Neuronal studies indicate that neurons are initially excited with a 1°C drop in temperature (99). However, during environmental hypothermia, not all neuronal cells are uniformly activated since the brain does not cool uniformly. Hayward and Baker (44) demonstrated a significant nonuniformity in temperatures in various areas of the brain in dogs, sheep, monkeys, and cats. In addition, the anatomical organization of the cortical neurons dictate which part is hyperexcitable. Neurons may have their extensions arranged in an anatomical fashion so that some of the extensions may become cold relative to other anatomical parts of the neuron. Thus, a neuron in the cortex or cerebellum that has vertical neuritic extensions from the nerve cell body, may have cold-induced hyperexcitable extensions that may induce multiple spikes (16).

Hypothermia progressively depresses the central nervous system (CNS). On the peripheral side, nerve conduction in man is decreased from 30 m/sec at 35°C to 12 m/sec at 21°C. These decreases partially explain the observed motor incoordination and decrease in manual dexterity (98). Cerebral metabolism has been reported to decrease linearly from 6% to 10% for each 1 degree decrease in temperature in the range of 35°C to 25°C (33,81). Significant attenuation and

frequency alterations in the brain's electrical activity can be observed at temperatures below 34°C (59,121,8). Continuous cooling of the brain has an effect on cortical functioning in a descending manner. Cerebral cortical function is initially impaired, with continued cooling affecting other brain structures in a descending fashion. When medullary cellular activity becomes suppressed, cessation of respiration follows. This blockage of the normal respiration rhythm can be reversed by warming the fourth ventricle (120). Complete absence of electrical activity (a flatline EEG) normally occurs at temperatures below 20°C.

In addition to the direct effect of cold on neuronal tissues, cooling the CNS influences localized blood flow and the integrity of the blood brain barrier. Appropriate autoregulation of cerebral blood flow is maintained until brain temperatures fall below 25°C. However, it is important to note that relative to other organ systems, a disproportionately high redistribution of blood flow is directed to the brain when profound hypothermia has occurred.

Mild hypothermia has been shown to reduce vascular permeability in cerebrally non-ischemic rats (56). In ischemic animals, decreasing cerebral temperatures minimized hypoxia-induced blood brain barrier abnormalities, whereas raising the temperature to 39°C had the opposite effect (27). In addition to the effects during the hypoxic-induced state, mild hypothermia reduced the degree of postischemic edema in gerbils after 40 minutes of bilateral occlusion (26). Overall, these studies suggest that hypothermia reverses the destabilizing effects of hypoxia on cell membranes.

From a clinical perspective, profound hypothermia is deliberately induced to minimize or prevent cerebral ischemic injury during certain types of cardiac and cerebrovascular surgeries (36,86,127). The circulation can be arrested for prolonged periods, exceeding 30 minutes without incurring severe cerebral injury (36,81,128). The beneficial effects of profound hypothermia classically have been attributed to a temperature-dependent reduction in metabolism (81,82,121). Under these conditions, the neural tissues tolerate prolonged periods of ischemia because their demand for oxygen is minimized.

Recent findings have suggested that significant cerebral protection may occur at mildly cold temperatures in the 33°C to 34°C range, similar to that which is well documented to occur with profound clinical hypothermia. Specifically, improved post-ischemic neurologic function has been reported in animal models in which mild hypothermia was instituted (14,89,63,85). It was also shown that improved outcomes following ischemia were apparent even when the hypothermia was induced either during or immediately after the occurrence of an ischemic event (14,63,89). In two of these studies, mild hypothermia induced cerebral protection, which was not correlated to a reduced production of lactate (i.e., reduced anaerobic metabolism) (14,63). Hence, a reduction in global cerebral metabolism, per se, does not appear to be an adequate explanation for the protective effects of mild hypothermia. It is hypothesized that the beneficial effects of mild hypothermia may not only be due to a reduction of metabolism, but also to: 1) temperature-induced alterations in ion homeostasis (including calcium); 2) increased membrane lipid stability; 3) alterations in the release and re-uptake of neurotransmitters (e.g., excitatory amino acids and dopamine); 4) preservation of the blood brain barriers (14,63,89,85); and 5) the release of various substances that have a protective effect on cellular membrane function.

MOTOR ACTIVITY

Hypothermia influences motor function by way of its effect on the neural system, vasculature, and on the muscle cell itself. When a person becomes hypothermic, muscle tension and shivering continues until core temperature reaches 29°C to 31°C. A significant preshivering tone normally precedes the occurrence of shivering. In part, it is this tonic activity that is the basis for the feeling of stiffness that most people experience when they get cold (21). Such motor tone has been reported to appear first in extensor and proximal muscles, which are the same muscles in which the amplitude of shiver is largest (101). Shiver has been defined as involuntary rhythmic waxing and waning muscular contractions used to maintain a normal body temperature (homeostasis) (47). These oscillations are modulated by myotatic reflex loops, since

deafferentation will cause the frequency characteristics of shiver to become irregular (86,100,101). From a thermogenesis point of view, shivering doubles heat productions. Due to the oscillatory nature of shivering, metabolic rates may vary from two to five times normal body heat production. During shiver, both agonist and antagonist muscle can be contracting periodically, but not necessarily reciprocally, (i.e., the muscle tension increases, but the limbs do not move effectively; hence, little or no work is done). The frequency of shiver varies from muscle to muscle, but is considered fairly low, between 5Hz and 10 Hz. If the antagonistic muscles were to be coactivated at higher rates or to elicit contracture (i.e., sustained force production without associated electrical activity), the heat that could be generated would be proportionally greater. However, a major drawback to this type of activation would be the high degree of resultant limb stiffness that would limit one's ability to make superimposed voluntary movements.

Numerous observations and data indicate that the underlying control mechanism for shiver has central and peripheral components. In the late 1950s, pure central shivering was shown to be produced by localized cooling of the hypothalamus (58,40). Lim reported that by reducing subcutaneous temperature of a dog from 33°C to 30°C, while maintaining a brain temperature of 38°C, evoked a shivering response (66). Consistent with these findings, it has been observed that humans placed in a 10°C environmental chamber for a period of 15 to 40 minutes demonstrate intense shiver even though their core temperatures remain the same or slightly increased (50). In addition, shivering may be decreased as a person does specific mathematical reasoning (75).

Increases and decreases in shiver amplitude and/or changes in duration have been documented to be altered by changes in inspiratory parameters. Inspiration of cold air has been shown to cause an increased rhythmic and tonic muscle activity, whereas inspiration of warm, humidified air can attenuate or stop spontaneous shivering (102). Although shivering generates heat and prolongs tolerance, it is not always desirable and may paradoxically influence a person's performance.

In many environmental situations, shivering is clearly undesired, e.g., when a deep sea diver is trying to perform a fine motor task. Attempts have been made to minimize the occurrence of such oscillations during diving by employing specialized (e.g., warmed) oxygen tanks to avoid hypothermia and prevent shiver.

Hypothermia affects the muscle directly. Clinical cases report that individuals with frozen limbs have been successfully rewarmed with no apparent long-term effect.

SLEEP

Of all the CNS functions, the one that may significantly affect human tolerance to the cold is sleep or the lack thereof. Little attention has been given to the sleep generating systems and its effect on thermal regulation. According to Opstad, sleep deprivation might affect thermoregulation as it affects other neural systems in which visual hallucinations, impaired balance, may occur (94). While the sleep cycle influences thermoregulation by altering fundamental mechanisms in the central nervous system, the ambient temperature also influences these cycles (116).

CARDIOVASCULAR SYSTEM

The cardiovascular system has received the most attention in studies of hypothermia since various surgical techniques, such as cardiac bypass surgery, have employed low body temperatures. Ventricular fibrillation or cardiac standstill is usually associated with hypothermia and is considered the main explanation of hypothermia-induced death. The reversibility of the cold-induced ventricular fibrillation or standstill is one of the major determinates of tolerance to the cold. However, cold, per se, does not cause ventricular fibrillation; rather cold-induced ionic alteration, such as hyperkalemia, may be the underlying cause (125,46).

Cold stress activates the sympathetic nervous system to cause peripheral vasoconstriction, which may result in hypertension, an increase in cardiac afterload on the heart, and an elevated myocardial oxygen consumption. These changes are often associated with an initial tachycardia. As an individual becomes moderately hypothermic, bradycardia and myocardial depression follow,

leading to a decreased cardiac output and hypotension. In mild hypothermia the variability in circadian heart rate is greater than during normothermia. This variability may be explained on the basis of an imbalance between the parasympathetic and sympathetic nervous systems (70). A decrease in heart rate by 50% can be recorded from individuals with core temperatures near 28°C (118). This bradycardia results from a spontaneously decreased depolarization of pacemaker cells and is refractory to atropine (104). At core temperatures below 32°C, atrial dysrhythmia occurs, secondary to atrial distension (72). Ventricular arrhythmias are commonly observed below 32.2°C. Primary ventricular fibrillation is rare at 32.2°C with maximal susceptibility between 28°C and 30°C (92). At core temperatures less than 30°C the heart is reported to be very sensitive to mechanical stimulation, and cardiopulmonary resuscitation efforts may convert a very slow sinus bradycardia to ventricular fibrillation in the severely hypothermic patient. As the core temperature approaches 25°C, fluid shifts out of the vascular space, which may increase the hematocrit by 150% (65). The ensuing hypovolemia and increased blood viscosity further compromise the cardiac output.

The electrocardiogram demonstrates significant changes with hypothermia. There is a prolongation of the PR and Q-T intervals and widening of the QRS complex. These changes are indicative of specific myocardial ionic activities that are influenced by the cold. Membrane currents are controlled by multiple processes that control the membrane channels. These channels are composed of lipoprotein whose activity are temperature dependent. Thus, low temperatures result in a slower activation and inactivation of different membrane currents and contribute to various electrophysiological changes. In turn, the rate of depolarization is reduced during hypothermia resulting in a widening of the QRS complex. The explanation for this phenomenon is that during hypothermia, the rate of the opening and closing of the sodium channels is decreased as well as the sodium channel conduction, which causes the reduction in the maximal rate of membrane depolarization. This phenomenon involves the complex interplay between

various ions, such as sodium and potassium, since these ions have common transport mechanisms.

Hypothermia also influences the repolarization phase of the action potential. A 1°C drop in myocardial temperature lengthens the cardiac action potential and refractory period by 15 to 20 msec and is due to alterations in various potassium currents. During phase I of repolarization, there is an early transient outward potassium current. During phase III, there is a time-dependent, delayed rectifying, potassium current simultaneous with a time-independent inwardly rectifying potassium current. Both of the potassium currents in phase III are considered temperature sensitive. Thus, if both of these repolarizing currents are reduced, a consequent lengthening of the action potential duration and refractory period occurs. Other inward currents, such as sodium and calcium may also be affected by the cold, and contribute to the lengthening of the action potential.

Following the depolarization of the myocardial cells, there is an opening of the voltage-dependent calcium channels causing an influx of calcium ions, which in turn, activates the release of calcium from internal storage in the sarcoplasmic reticulum. Next, intracellular free calcium binds to contractile proteins, which actively allows for muscle contraction (32). During the initial stages of hypothermia, systolic contractile force and intracellular calcium increase. This is due either to increased levels of free cytosolic calcium or to the sensitivity of the contractile proteins to calcium. Some investigators contend that cardiovascular collapse during hypothermia is due not to myocardial contraction, but rather to some arrhythmia (137).

Cold-induced cardiac arrhythmias may be caused by several possible mechanisms. One hypothesis (circus theory) proposes that either a nonhomogeneous conduction and/or refractoriness may exist. According to this theory, there is a greater increase in conduction time than in refractory period. Such an increase in the conduction time/refractory period ratio makes re-entry currents possible, thereby initiating ventricular fibrillation (52). There may be areas with different temperatures which could cause disproportionate changes in

refractory periods and conduction times. These cold-induced changes could easily produce multiple ectopic sites eventually resulting in ventricular fibrillation.

Cold also affects the atrium and ventricles differently. Since the speed of conduction is greater in the atria than in the ventricle, the pacemakers of the atrium are able to maintain normal synchronized muscle contraction at much lower temperatures. In the case of the ventricles, since the conduction velocity in the Purkinje fibers is slower even at normal temperatures, they are more susceptible to being inhibited by the cold, allowing the ventricular myocardium to contract irregularly, promoting multifocal ventricular tachycardiac sites and eventually fibrillation. This difference in susceptibility is seen in rat hearts that have been stored at 4°C for 0, 12, and 24 hours.

Due to the importance of cold-induced ventricular fibrillation, much research has focused on the effect of cold on cardiac muscle and the conducting system in the heart. The effect of cold on the coronary circulation is not fully understood. There is little evidence that cold stress influences the responsiveness of the coronary arteries (91). However, it is well-recognized that angina pectoris (constriction of coronary arteries) can be either precipitated or worsened by cold exposure (43). Although it has been presumed that cold increases the metabolism of cardiac tissues by neural mechanisms, this hypothesis has not been rigorously substantiated. In summary, the coronary circulation appears to respond to a cold stress as it would whenever cardiac output and systemic pressure increase through activation of the sympathetic nervous system.

RESPIRATORY SYSTEM

The initial respiratory response to cold stress is a significant increase in rate (i.e., hyperventilation) followed by a decrease (hypoventilation) (Table 3). Skin temperature afferents can influence respiratory function dramatically. The hyperventilation is followed by a progressive decrease in the respiratory minute volume that is proportional to the decreasing metabolism. The neurocontrol of respiration becomes compromised as the function of the brainstem is impaired by severe hypothermia. Respiratory rate falls from 7 to 15 breaths

per minute (bpm) at 30°C to 4 to 7 bpm at temperatures in the mid 20s (61). Eventually retention of carbon dioxide by the tissue leads to respiratory acidosis. In most cases of severe hypothermia, respiration diminishes and the heart continues to contract for some period of time (54).

Anatomical and functional physiological respiratory dead space are increased in hypothermia (115) whereas individual alveolar dead space does not change. Stimulation of respiratory drive by both carbon dioxide and hypoxia is absent at 20°C (127). During moderate hypothermia, in an absence of shiver, a reduction in oxygen consumption is associated with a parallel reduction in carbon dioxide production. Thus, what would be considered low levels of oxygen pressure in normothermic environments would be adequate at hypothermic levels. Although the arterial content of carbon dioxide is low, its solubility has increased.

As the individual becomes hypothermic, several other physiological factors associated with respiratory function occur. These include: 1) a decrease in ciliary motility; 2) bronchorrhea; 3) an increased potential for noncardiogenic pulmonary edema as fluid shifts occur (19); 4) an alteration in the contractile function of the diaphragm and intercostal muscles; 5) a decrease in lung compliance; and 6) a decrease in the elasticity of the thorax. Pulmonary circulation time is usually prolonged unless there is intrapulmonary shunting.

Although hyperventilation is associated with cold stress, cold-induced respiratory arrest also occurs. This reflex may be important in subjects who suffer from submersion hypothermia. Such a response causes the person who is submerged to involuntarily aspirate water and consequently drown. The cold water aspirate consequently cools the brain and heart rapidly, because the heart continues to effectively beat for five minutes after aspiration. The blood is subsequently cooled since it is circulated in the pulmonary cold water environment, dropping cerebral and cardiac temperatures. This internal cooling is considered the explanation of the complete recovery of victims who experience cold water near drowning. Consideration of tolerance to submersion hypothermia must include the respiratory system. When a person drowns in cold water, there are approximately 45 minutes during which the victim may be revived. This effect

is due to cooling of the core by cold water in the lungs while the heart continues to beat. The cold water, in contact with the pulmonary vasculature, and the continuous heart beating, promotes a rapid internal cooling of the internal organs, such as the brain and heart. This allows the brain to survive hypoxia for approximately 45 minutes. This form of cooling is more effective in children than adults. More than likely this is due to the smaller mass and large surface area to volume ratio that children have.

RENAL

Diuresis is one of the early consequences of an exposure to the cold, which becomes prominent even before core temperature has decreased. There are two proposed mechanisms for this cold-induced diuresis (39). One theory suggests that the cold-induced diuresis is an autoregulatory response of the kidney to a relative central hypervolemia induced by peripheral vasoconstriction. Additionally, the release of antidiuretic hormone is suppressed, as the kidney is faced with a volume overload. The subsequent cold-induced diuresis decreases the blood volume so that progressive hemoconcentration develops. Cold-induced diuresis may be due to osmotic alteration in the renal tubules. Eventually, renal function is depressed during hypothermia due to a fall in systemic blood pressure and the indirect effect of the cold on organ metabolism itself. As the renal blood flow decreases, renal vascular resistance rises, promoting a further decrease in renal flow and a subsequent decrease in glomerular filtration. During hypothermia, renal oxygen consumption is more rapidly reduced relative to other organs, such as the liver, heart, brain, skeletal muscle, and skin. Serum sodium, calcium, chloride, and potassium concentrations remain in the normal range until core temperature is 25°C, but due to the cold-induced depression of the renal tubular function, sodium and water reabsorption are reduced, promoting a pronounced osmotic diuresis (62). Faced with continuous hypothermia, an additional large shift of body water will occur. Whether the cold-induced diuresis is explained on the basis of volume overload or ionic imbalances, it is a major concern. For example, cold water immersion has been shown to increase urinary output 3.5 times and this may be a contributing factor to the "rewarming

shock" that occurs following active vasodilation induced by rewarming treatments (22).

Potassium ion regulation may be impaired in hypothermia. Hyperkalemia, one of the leading causes of cardiac dysrhythmia (119), is usually an ominous sign of tissue hypoxia (93).

BLOOD

As the cold decreases cellular function, the amount of oxygen available remains constant since the oxyhemoglobin dissociation curve shifts to the left. This shift dictates that the partial pressure of oxygen must fall to lower values before hemoglobin gives up its oxygen (96). In the face of hypoxia, cells shift to anaerobic metabolism resulting in a metabolic acidosis. As the hydrogen ions enter the blood, they shift the oxygen dissociation curve to the right which promotes the unloading of oxygen.

Furthermore, both oxygen and carbon dioxide are more soluble in cold blood (96). Compared to normothermic values, the solubility of oxygen is increased by 33% at 25°C. However, this increase in solubility cannot be considered an added benefit until the tissue has a temperature of 16°C (90).

In addition, hypothermia prolongs clotting time. Hypothermia causes an increase in bleeding time since the platelets are sequestered in both the portal circulation and the liver (130). In addition to thrombocytopenia, an elevation in hematocrit and viscosity occurs (18).

ACID-BASE BALANCE

Acid-base balance in hypothermic situations differs from that of normothermia. After an initial respiratory alkalosis from hyperventilation, the more common underlying disturbance is a relative acidosis. Acidosis has both respiratory and metabolic components. In addition, as the temperature decreases, the solubility of carbon dioxide in blood increases. Metabolic acidosis is produced by impaired hepatic metabolism and acid excretion, lactate generation from shivering, and decreased tissue perfusion. Due to the variety of underlying causes of hypothermia, clinical prediction of acid-base status is not possible. In one series of 135 cases, 30% were acidotic and 25% alkalotic (83).

Confusion persists regarding arterial blood gas correction relative to the reduction in core temperature. Initially the pH was corrected to normal body temperature to aid in the clinician's interpretation of the pathophysiology involved in hypothermic arterial oxygenation and acid-base balance (111). Historically, this process created problems. If a pH electrode could be used at the patient's current core temperature, an uncorrected but exact pH value would be obtained. However, arterial blood samples are always warmed to 37°C before electrode measurements are obtained, and are not measured at the patient's subnormal temperature.

Optimal strategy to maintain acid-base homeostasis during treatment of accidental hypothermia is still evolving (135). The accepted earlier assumption was that 7.42 is the ideal "corrected" patient pH at all temperatures, and that therapy should be directed at maintenance of the corrected arterial pH at 7.42. The rationale for this pH approach termed "endothermic" has been questioned (134). A better intracellular pH reference may be electrochemical neutrality, in which pH = pOH. Since the neutral point of water at 37°C is pH = 6.8, Rahn (106) has hypothesized that this normal 0.6 unit pH offset (7.42-6.8) in body fluids should be maintained at all temperatures. Since the neutral pH rises with cooling, so should blood pH. This pH approach, termed ectothermic, is commonly followed.

Rahn observed that Antarctic codfish survive far below the freezing point of water due to a presence of a glycoprotein that minimizes formation of ice crystals (antifreeze) and they function in an extremely alkalotic state. This same blood pH variation (i.e., a rise in pH with a decline in temperature) is seen in other cold-blooded vertebrates and invertebrates.

Several experimental and clinical studies support Rahn's hypothesis (106). In one study, a set of puppies with pH maintained at 7.4 had a 50% drop in cardiac performance after bypass. The control group, left alkalotic, had normal cardiac indices and increased cerebral blood flow (7). In other canine studies, during systemic deep hypothermia, constraining the corrected pH to 7.4 caused myocardial damage whereas relative alkalinity afforded myocardial protection

(124). Other advantages of the relative alkalinity include improved electrical stability of the heart. The fibrillation threshold of dogs markedly decreased when arterial pH was held at 7.4, but was unchanged with alkalosis. In contrast, maintaining the pH at 7.4 during hypothermia in a rat model did not affect cardiac work response (117). This suggests that the optimal range for extracellular pH is large in some species.

In a recent study of 181 cardiac bypass patients, 121 consecutive cases were "endothermically" managed with corrected normal pH and PCO2 values. Ventricular fibrillation occurred in 49 (40%). In the other 60 cases left "ectothermically" alkalotic, only 12 patients (20%) developed spontaneous ventricular fibrillation (57).

These observations provide some evidence in support of Rahn's hypothesis that the advantage ectotherms obtain with a constant relative degree of alkalinity also applies to warm-blooded endotherms during hypothermic conditions. Potentially deleterious effects of this alkalosis on other organ systems have yet to be identified. However, it is clear that maintaining the corrected pH at 7.4 and PCO_2 at 40 mm Hg during hypothermia depresses cerebral and coronary blood flow, cardiac output, and increases the incidence of lactic acidosis and ventricular fibrillation. Correction of pH and PCO_2 in hypothermia is unnecessary and potentially deleterious.

FLUIDS, ELECTROLYTES

Dehydration is associated with all forms of hypothermia with free-water depletion elevating serum sodium and osmolality. Since hypothermia produces natriuresis, saline depletion may be present (72).

Blood viscosity increases 2% per degree C temperature drop, and hematocrits over 50% are seen. Low circulatory plasma volume is often coupled with elevated total plasma volume during rewarming (42).

Infusion of fluid does not always reverse cold-induced fluid shifts. In one experiment, normal saline had minimal lasting effects and did not hasten cardiovascular recovery from hypothermia (108). In another, 10% low molecular

weight dextran solution increased plasma volume and decreased blood sludging (28).

In some cases, rapid volume expansion is critical (23). For example, in neonates, adequate fluid resuscitation markedly decreases mortality (126).

GASTROINTESTINAL PHYSIOLOGY

In general, smooth muscle motility throughout the gastrointestinal system decreases as core temperature falls. As a consequence, acute gastric dilatation, paralytic ileus, and distension of the colon occur. Also, all gastrointestinal secretions and free acid production are depressed (72). It is commonly observed that the pancreas and the gastric mucosa are major sites of cold associated hemorrhages called "Wischnevsky's lesions" (74). These lesions are seen in 80% of hypothermic victims and are of greater severity in the younger individuals. A possible explanation for these lesions is they are a result of the reperfusion after cold-induced collapse of the microvasculature. Hypothermia causes a catecholamine-induced vasoconstriction of blood vessels and release of corticosterone, which can be ulcerogenic. Eventually catecholamine secretion is decreased promoting a vasodilation which results in significant reperfusion and eventual extravasation of blood. In some undetermined manner, the changes in the microcirculation alter the gastric mucosa's protective mechanism, resulting in cellular damage induced by hydrochloric acid.

Associated with hypothermia is a decrease in splanchnic blood flow, which may be greater than a proportional fall in cardiac output (6). Liver cells continue to respire, but are not able to utilize glucose. Associated with the depression of liver function will be a significant decrease in its ability to rid the body of metabolites, drugs, or conjugate steroids.

ENDOCRINE SYSTEM

Hypothermia is a major stressor and evokes a widespread hormonal response. Exposure to cold will stimulate the release of catecholamines which will stimulate thermogenesis (129).

Corticosteroids become elevated. There is an inverse relationship between the concentration of 11-Hydroxycorticosteroids in plasma and the depth of

hypothermia. In one report, the highest concentrations of corticosteroids were measured in individuals who died while hypothermic (96.4 ug/dl), while those who died three days later had values of 87.1 ug/dl, and those who survived had the lowest levels of 62.9 ug/dl (71). However, in another study, Stoner et al (122) were unable to find any correlation between plasma cortisol concentration and temperature with respect to survivability. Consequently, its role in promoting tolerance is not established. Thyroid-stimulating hormone (TSH) and thyroid hormone concentrations have been recorded as normal in hypothermic patients. With rewarming, T4 and T3 concentrations decreased: T4 concentrations were 8.2 ug/dl and decreased to 7.0 ug/100dl and T3 concentrations went from 155 ug/dl to 138ug/dl (138).

Insulin concentrations in hypothermic patients are also varied. Insulin's role in facilitating the transport of glucose becomes inactive below 31°C, and yet, at these temperatures blood glucose concentrations are noted to be variable. Prescott (103) reported that some hypothermic patients were actually hyperglycemic, although this was associated with diabetes (severe ketoacidosis) being a predisposing condition. In general, the blood glucose concentration depends primarily on the metabolic state of the patient and not on the degree of hypothermia. This issue is far from resolved since pancreatitis is a common finding at autopsy in hypothermia (112). The extent of hyperglycemia is proportional to the degree of body cooling. The hyperglycemia is due to: 1) increase in catecholamine secretion, 2) decrease in insulin activity, 3) decrease in renal clearance of glucose, 4) decrease in liver enzyme function, and 5) increase in catecholamine-induced glycogenolysis. Information concerning protein and fat metabolism during hypothermia is lacking (127).

Ethanol injection inhibits glucose-induced insulin secretion and stimulates pancreatic glucagon secretion. Overall, ethanol will lower blood glucose concentration and impair gluconeogenesis. Hypoglycemia associated with exercise will promote a faster rate of hypothermia (37).

IMMUNE SYSTEM

In most considerations of hypothermia, the effect on the immune system is rarely considered. In a real-life scenario, most cases of hypothermia are associated with infections which might compromise the tolerance of the victim. In controlled cold stress or hypothermic studies either in laboratory or field experiments in which the subjects were previously screened for dehydration, sickness, the subjects rarely become sick. However, in either hospitals or field operations in which various stressors may interact to compromise the immune system, hypothermia and infection go hand-in-hand.

Everyday experiences demonstrate that decreased ambient temperature inhibits immune function. When an athlete injures a joint, for instance, ice is used to prevent the infiltration of immune cells and the subsequent release of inflammatory cytokines. Conversely, heat can be applied to abscesses to speed healing at those sites. A more dramatic example would be the high propensity of leukopenia and bacterial infections in children kept hypothermic for clinical reasons (13). Yet recent breakthroughs in immunology have not been cohesively integrated with existing knowledge of hypothermic sequelae. A small number of sources examine consequences of decreased temperature to immune function. In this section, the effects of cold on specific cellular components of the immune system will be discussed, then the role of the local environment in cold-induced immunosuppression will be explored.

Fever, historically, has been deemed to augment immune function (55,107). Hyperthermia of merely 2°C above normal has been shown to transiently raise the mononuclear cell count in cancer patients and increase the mitogenic response (97). Therefore, an increase of body temperature, whether induced or spontaneous, confers an advantage to the immune response.

On the contrary, decreases in ambient temperature are actually detrimental to immune function, as opposed to having a neutral effect (107). Sessler demonstrated that wounds are larger in guinea pigs infected under hypothermic conditions than those infected under control conditions (113). Since more than one half of the body volume is 1 inch from the surface and significantly cooler

than the core body temperature of 37°C (133), local skin temperatures may influence the growth of infections. Also, certain infections only occur in cooler parts of the body; for example, rhinoviruses grow optimally at 33°C and primarily infect the respiratory tract (109).

One potential explanation for cold-induced immunosuppression is that the immune cells themselves are specifically inhibited by decreased temperature. In cases of accidental hypothermia, when compensatory mechanisms become inadequate, certain observations can be made about the effect of cold on specific populations of immune cells. Histamine release from mast cells is decreased at low temperatures (110), and Biggar et al. (9) showed neutrophils were impaired in their migration both in vivo and in vitro. When the cooled cells were rewarmed they returned to optimal activity. In teleosts, repeated cold stress has been shown to decrease B and T cell functions (10).

Wang-Yang et al. (132) showed that some in vitro responses of helper T cells in mice are inhibited by cold, but that B cells were not similarly suppressed. However, cold interfered with interleukin (IL) production in virgin T helper cells, implying an early block in the activation of these cells. Interestingly, the responses of these cells in IL-2 and IL-4 were not affected by cold. Buttke (15) proposed that decreased fatty acid synthesis may be responsible for the inhibition of murine helper T lymphocytes at 27°C. Interestingly, B cells showed a greater conversion of stearic acid from 18:0 (18 carbon atoms, no double bonds) to 18:1 (18 carbon atoms, 1 double bond), and this is the purported reason for the lessened temperature sensitivity of this population.

When cold stress is applied to a whole organism, specific changes in the cellular components can be observed. Sundaresan and colleagues (123) showed that when albino rats were subacutely stressed with cold water immersion, the total number of immune cells was initially expanded. Total white cell count was increased, as well as total number of eosinophils and basophils. Phagocytic and avidity indices were also increased in phagocytic cells. However, Cheng et al. by demonstrating a decreased number of thymocytes and splenocytes (20), showed

that prolonged cold water stress actually has an immunosuppressive effect, as well as diminished blastogenesis of T cells and lowered natural killer cells activity. Macrophages were found to be less responsive to interferon-gamma, and because these antigen-presenting cells are crucial for initiating immune cascades, the impairment of macrophage function could be a significant cause of a dampened immune response. While the mice in the Cheng experiment were obviously also stressed by anxiety and exercise, these results still have implications for many settings of human accidental hypothermia. Aarstad (1) reconfirmed the results of Cheng in that an absolute value of CD4+ cells (most commonly considered helper T cells) was affected by cold stress, but not those of CD8+ cells (most commonly considered killer T cells). In the Aarstad (1) experiments, the number of stressors per day, as well as the duration of the trial, were varied and had an effect on the various populations of cells. For example, mice stressed once a day actually showed an increase in the percentage of CD4+ cells, while the mice stressed twice a day showed a decrease.

One of the most compelling yet most challenging aspects of immunology is to understand the way that the individual parts integrate into a functional whole. Limited studies have addressed this issue. Corticosteroids, which are released during cold stress-induced hypothermia, have a well-documented immunosuppressive effect (2).

It has been the premise of this section that in hypothermic settings the immune system is significantly impaired. However, same studies indicate that antibody-antigen interactions may actually be stronger at colder temperatures. Further, the optimal working temperature of complement is said to be 20°C to 25°C (109). However, as was pointed out above, many of the cell-mediated responses and the microenvironmental conditions necessary for those processes are made defective by cold. To reiterate, two of the more important players for initiating an immune cascade, helper T lymphocytes and macrophages, are specifically inhibited by cold.

Also, there are established microvasculature changes to cold, both local and global. Viscosity of the blood increases with cold, due in part to the

aggregation of red blood cells and the increased adhesion of white blood cells to the endothelium (30). Capillary occlusion is possible, leading to hypoxic damage. Endrich et al. (30) report a result different from many others, namely an observed increase in the permeability of the vessels to macromolecules, and some leukocyte extravasation before the increased adherence of these cells. It is clear that cold affects the immune response not only by inhibition of specific cells but also through microenvironmental changes, such as alterations in viscosity of the blood and permeability of the vessels.

REWARMING - EXTENDING TOLERANCE LEVELS

The initial focus of this chapter has been on the effects of cold in inducing a reduction in cellular metabolism which subsequently affects various systems. Rewarming has been able to reverse successfully these physiological processes. At present, various rewarming strategies are utilized for hypothermic patients. Most are effective and play a key role in increasing a person's survival after becoming hypothermic. However, rewarming does not always lead to survivability despite an increase in core temperature. Depending on the kind of hypothermia and its duration, the reduction in core temperature can be reversed (Figures 1 and 2).

The key decision is the choice between passive and active rewarming. In general, noninvasive passive external rewarming (e.g., blankets) is ideal in mild cases of hypothermia (31).

Options for active external rewarming include forced-air, electric or plumbed heating blankets, radiant heat sources, and immersion. Concerns with active rewarming include thermal injury to hypoperfused vasoconstricted skin, appropriate cardiovascular monitoring, and accessibility of therapy.

Sufficient endogenous thermogenesis is usually not possible below 32°C because of progressive hypothermia. Sufficient stored fuels, including glycogen, must be present to maximize (250 to 100 Kcal/hr) the effectiveness of shivering thermogenesis. In these situations, active rewarming is utilized.

Active rewarming of the core involves the direct transfer of exogenous heat to the patient bypassing the skin and directly heating the core. Active core

rewarming techniques include airway rewarming, heated infusions and irrigation, diathermy, and extracorporeal rewarming. Conditions which mandate active rewarming include cardiovascular instability, poikilothermia, thermoregulatory dysfunction, and endocrinologic insufficiency. Patients at the extremes of age also often require exogenous heat for recovery. Traumatic or toxicologically induced peripheral vasodilatation also obviates passive rewarming (24).

Airway rewarming with heated, humidified oxygen less than 45°C can be a valuable adjunct (67). Complete humidification is recommended to maximize the limited amount of transferrable heat, which is greater via endotracheal tube than via mask. Humidified airway rewarming decreases the viscosity of pulmonary secretion and cold-induced bronchorrhea, while stimulating pulmonary cilia and suppressing shiver. With this therapy, hypothermic ventilation-perfusion mismatch, depressed respiratory minute volume, and atelectatic changes are attenuated as is respiratory heat loss. In addition, the demands for oxygenation are addressed with this technique.

Direct application of heat to the extremities acutely extinguishes peripheral vasoconstriction and may overwhelm a depressed cardiovascular system with volumetric, metabolic, and electrolyte flux demands (114).

Another concern with rewarming is core temperature afterdrop, which is the continued reduction in the core temperature after initiating rewarming. This primarily results from progressive temperature equilibration between the shell and core coupled with reversal of the arteriovenous shunting in the extremities (25).

To assist with active therapy, intravenous fluids and blood should be heated to 40°C to 42°C (51). For example, 1 liter of fluid at 42°C infused into a 70Kg patient (60% total body weight) at 28°C will raise the core temperature 1/3°C. Rapid central administration of fluids should be avoided, since myocardial thermal gradients may induce arrhythmias or even fibrillation. Of interest, amino acid infusions have a thermogenic effect (increased oxygen consumption and energy expenditure) in some metabolic states. This may prove useful during recovery from accidental hypothermia.

The quantity of heat transferrable via irrigation varies with the site selection. Peritoneal dialysate at 40°C to 45°C efficiently conducts heat to the intraperitoneal structures. A double catheter system with outflow suction can exchange 6L/hour, which accelerates the rate of rewarming around 2°C/hour (64).

Irrigation of the chest via afferent and efferent thoracostomy tubes may also be valuable (38). Mediastinal irrigation and direct myocardial lavage should be limited to cardiac arrest situations. Direct gastrointestinal irrigation often induces fluid and electrolyte fluxes. In this case, as well as in bladder irrigation, heat transfer is very limited.

Diathermy is also being evaluated as a rewarming adjunct (136). Heat is transmitted via conversion of ultrasonic and low-frequency microwave energy to deep tissues. Dosimetry guidelines are being refined. Truncal applications appear ideal, unless metallic implants or significant edema are present.

Lastly, extracorporeal rewarming and hemodialysis are lifesaving modalities in profoundly cold victims in cardiac arrest (131). Heated oxygenated blood at flow rates up to 6L/minute can achieve a rate of rewarming averaging 9.5°C. These techniques are used in patients with completely frozen extremities, and those with severe rhabdomyolysis with major electrolyte disturbances.

SKIN - PERFUSION AND REPERFUSION STUDIES

Skin cells are traditionally very resistant to freezing. Although they may freeze, with proper rewarming they are able to be returned to normal function.

Studies concerning frostbite are important since they provide important information concerning how cells may be able to withstand actual freezing. Such studies hold the promise of extending hypothermic tolerance for the entire organism.

Meryman's (80) concept of freezing represents the removal of pure water from solution and its isolation into biologically inert foreign bodies, the ice crystals. He concluded that in extracellular freezing, the first ice forms outside the cells and is then augmented by intracellular water, which diffuses through the cell wall and condenses on the ice surface because of the high osmotic pressure of the extracellular solution that has been concentrated by

freezing. The temperature of the intracellular fluid never falls below its freezing point, since intracellular water is continuously being lost with a corresponding continuous reduction in freezing point. Karow and Webb (53) further noted that water cooled below 0°C does not crystalize until a temperature is reached that will permit the utilization of substances within the water to act as a site for ice formation. The nuclear material may be relatively large inclusion bodies, such as colloids, dissolved substances, or it may simply be molecules clumped together by hydrogen bonds (e.g., the microcrystals). They suggest that in slow freezing, a tendency exists for water and cells to supercool, since there is a low probability that such a minute volume would contain a nucleation center. Supercooling is a cooling of a substance below the temperature at which a change of state would ordinarily take place, but without such a state occurring; for example, the cooling of a liquid below its freezing point in which freezing does not occur. This results in a metastable state, defined as an excited stationary energy state whose lifetime is unusually long. At relatively high temperatures (-10°C), extracellular water freezes. As water freezes in the external medium, its vapor pressure reduces that of the still supercooled intracellular water and thus draws free water from the cells.

Luyet et al. (69) studied the invasion of living tissue by ice and listed three states of invasion: 1) superficial freezing, 2) intercellular freezing (extracellular spaces), and 3) intracellular freezing (cytoplasm). He demonstrated erythrocytes shrinkage by osmotic degeneration in intercellular freezing.

Meryman (79) considered salt concentration as a cause of injury when salt denaturation of membrane components occurred. He suggested that the primary site of cell injury was the cell plasma membrane, which includes alterations in membrane permeability, along with the effect of elevated extracellular osmolality, resulting in loss of cell water and reduction in cell volume.

Mazur (77) reviewed the responses of living cells to ice formation and considered that although the freezing point of cytoplasm is usually above -10°C, cells generally remain unfrozen and therefore supercooled to -10°C or

-15°C, even when ice is present in the external medium. This indicated that the cell membrane can prevent the growth of external ice in the supercooled interior and further suggests that cells do not contain effective nucleators of supercooled water. Mazur believes that to understand the role of intracellular hypertonic solution in the mechanism of cell damage, one must consider the four discrete events that occur during freezing: 1) water moves extracellularly to form ice, 2) nonpermeable intracellular solutes of high and low molecular weight concentrate, 3) cell volume decreases, and 4) solutes precipitate. However, Mazur disagrees with the theories of Lovelock (68) and Meryman (79). Mazur considers the cause of injury from extracellular ice to be due to recrystallization of ice crystals which exert sufficient force to rupture the plasma membranes and/or the membranes of organelles, such as mitochondria. His rationale for this suggestion is that recrystallization can disrupt protein gels, and that cells killed by intracellular freezing have suffered membrane damage and become leaky.

As a result of studies of cold-induced morphologic changes in vascular endothelium of the skin, Marzella et al. (76) proposed a nonthermal explanation of ice-induced cell damage. He concluded that the endothelial cell is the initial target of the injury induced by freezing, and concluded further that the injury is mediated by a non-free radical mechanism. The statement is made that "by now it is generally agreed that direct thermal injury alone is not sufficient to cause cell death" (76). Marzella believes that the initial freezing impairs the microvascular function, leading to edema, stasis, thrombosis, and finally ischemic necrosis. Subsequent thawing activates the production of arachidonic acid metabolites, which can cause inflammatory responses. These reactions will modulate vascular contraction and permeability, platelet aggregation and recruitment, and activation of leukocytes. These responses are, in turn, thought to promote production of free radicals in the induction of tissue damage. Marzella (76) pointed out that the consideration of free radical-induced injury has been supported by evidence showing that superoxide dismutase and iron chelate administered at the time of tissue thawing protects against frostbite damage.

Physiologic and biochemical evidence also exists from other experimental systems suggesting that endothelial cells are highly susceptible to hypothermia-induced free radical-mediated injury.

However, in Marzella's model (a rabbit) freezing caused an immediate separation of endothelial cells from the internal elastic lamina. It was considered that the separation was present even in samples removed immediately after freezing and before skin thawing, so that blood reperfusion could not be considered responsible for that lesion. Separation of endothelial cell junctions was observed in both venules and capillaries soon after freezing. It was considered that inflammatory mediators released after injury, such as leukotrienes, contributed to separation of cell junctions.

It has been demonstrated that with slow tissue freezing, ice crystal formation is generally confined to the extracellular spaces. However, cells once frozen, may upon thawing and refreezing, demonstrate uniform crystallization intracellularly, with formation of large, destructive crystals of ice. This result is considered lethal. This may account for the disastrous freeze-thaw-refreeze injury seen clinically; after initial extraction of cellular water, with increased permeability and trauma to the cell membranes or endothelial lining of small vessels, a second freeze will crystallize intracellular supercooled water, resulting in the destruction of the cells (78,84,77,41).

Mundth (87,88) demonstrated platelet clumping soon after thawing, arising from injured endothelium followed by corpuscular aggregation that eventually became occlusive. Mundth (88) recognized that local tissue injury from freezing was associated with local vascular damage after thawing, involving increased endothelial permeability, intravascular cellular aggregation, capillary stasis, occlusion of small vessels by cellular aggregates, and thrombosis. He demonstrated that low molecular weight dextran (m.w. 41,000) given intravenously prior to freezing, improved tissue survival after freezing. It was associated with improved capillary flow and inhibition of corpuscular aggregation. This work was confirmed by Anderson and Hardenbergh (5), but only when test animals were rapidly thawed after freezing.

Carpenter et al. (17) demonstrated the beneficial effects of rapid rewarming at 42°C, showing that by such methods, endothelial cells remained attached to the arterial intima, the internal elastic lamina was intact, and the medial wall was less distorted. During slow thawing, the endothelial cells were almost completely shed into the vascular lumen, the internal elastic membrane was disrupted, and medial cells were distorted and necrotic.

SUMMARY

With the advent of sophisticated rewarming techniques, physiologic systems demonstrate great tolerance to hypothermia. Organs can be cooled, and in some cases frozen, leading to a decrease in metabolic demands and then rewarmed with little or no long-term damage. In this chapter, the changes occurring in each system as it becomes cooled have been briefly presented. Additional research is required to ascertain how different physiological systems react as they are rewarmed.

Not all cases of hypothermia are reversed with rewarming. The major challenge for extending the limits of tolerance to hypothermia is to ascertain the fundamental mechanisms that are unleashed upon rewarming. The microvasculature remains the key site for extending human tolerance to hypothermia. The currently favored hypothesis for frostbite-induced damage is that free radicals are released by reperfusion that subsequently alter vascular tone. Eventually, these changes cause failure of the microcirculation and endothelial cell damage, resulting in thrombosis and necrosis (73,11). It is probable that the same cascade of events that occurs in frostbite also occurs during rewarming of the hypothermic patient. Predicting which system will fail upon rewarming is difficult since in many cases the hypothermia is secondary to some underlying pathology.

The reversal of hypothermia continues to be a challenge for investigators and clinicians. As the interaction of cold-induced cellular mechanisms from various organ systems is more completely understood, tolerance to hypothermia will continue to be prolonged.

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FIGURE AND TABLE LEGENDS

FIGURE 1: The hypothetical fall in core temperature during primary hypothermia can be successfully reversed at various points, depending on the core temperature. Arrows represent a reversal of hypothermia by various methods.

FIGURE 2: The hypothetical fall in core temperature during secondary hypothermia can be successfully reversed. However, due to underlying pathophysiological conditions, the range of unassisted recovery is much shorter than in Figure 1. Arrows represent a reversal of hypothermia by various methods.

TABLE 1: Core Temperature Definitions of Hypothermia

Certain core temperatures which are used to define the depth of hypothermia and the effectiveness of rewarming methods are presented.

TABLE 2: Various Kinds of Hypothermia and Associated Physiological Factors

The various types of hypothermia and associated physiological factors with tolerance times are presented. Most types of hypothermia included other physiological factors (e.g., anoxia, dehydration) which influence tolerance times.

TABLE 3: Effects of Decreasing Core Temperature on Physiological Functions

Changes in core temperature will have specific effects on various physiological systems. As core temperature falls this associated decrease in physiological function will influence tolerance times.

Acknowledgements

The authors would like to acknowledge the outstanding editorial assistance of Ms. S. Sobanski and the significant contribution of Ms. T.C. Pozos. We would also like to acknowledge the partial support of Augustine Medicine Foundation for support of this manuscript.

TABLE 1: Core Temperature Definition of Hypothermia

Type	Range	Signs
Mild Hypothermia	36-33°C	Individuals remain conscious and will normally recover spontaneously without interventions once they move to a warm environment.
Moderate Hypothermia	33-25°C	Individuals usually lose consciousness; they can be successfully rewarmed by external means.
Profound Hypothermia	Below 25°C	Vital signs, such as heart rate and ventilation rate, are greatly reduced or absent. Individuals may be effectively rewarmed with minimal long-term effects. Requires intensive clinical management. Individual is unconscious.
Profound Clinical Hypothermia	Below 22°C	Individual is placed on cardiopulmonary bypass, and his/her core temperature is rigidly and effectively reduced to values below 22°C.

TABLE 2: Various Kinds of Hypothermia and Associated Physiological Factors

TYPE	DESCRIPTION	PHYSIOLOGICAL FACTORS	TOLERANCE
Immersion Hypothermia	The rapid induction of a hypothermia state due to the conductive properties of water (i.e., heat loss via immersion can be 40 times greater than by air at a given temperature).	fatigue; hypothermia; hypoglycemic	Survival Suit 6-hours; no suit 45 minutes
Submersion Hypothermia	Refers to the situations in which a person drowns in cold water.	anoxia; hypothermia	45 minutes
Mountain Hypothermia	A person has become hypothermic in an environment with reduced oxygen.	hypoxia; fatigue; hypoglycemia; hypothermia	Days
Divers Hypothermia	These individuals can become hypothermic from the inside-out by breathing cold dry mixtures of gases, which may include helium.	hypothermia; fatigue; hypoglycemia	Hours
Exercise-Associated Hypothermia	Confounding factors, such as dehydration and/or depleted energy stores (causing fatigue), predisposes the individual to the risks of becoming hypothermic.	dehydration; fatigue; hypoglycemia	Hours, days
Elderly Hypothermia	Refers to hypothermia induced in an individual whose thermoregulatory mechanisms have degraded with age, thus becoming cold stressed by previously innocuous environments.	dehydration; hypoglycemic	Years
Pediatric Hypothermia	Commonly occurs in neonate or a child exposed to an environment which is not stressful to an adult. They have a small body mass (heat generator), but a proportionately larger surface area from which to lose heat.	hypothermia; hypoglycemic	Hours, days

TABLE 3: Effect of Decreasing Core Temperature on Physiological Functions

Cardiovascular system	°C	Respiratory system	°C	Renal function
Peripheral vasoconstriction	37	↑Resp. rate; resp. alkalosis bronchospasm	37	Cold diuresis (x2-2.5)
↑ HR ↑ BP ↑ CO Centralization of blood volume	36	Immersion: initial gasp + hypervent. (x5)-hypocapnia	36	RBF & GFR →
	34	Resp. shallow	34	
BP difficult to obtain J-wave		Bronchorrhea		FF slightly ↑
Prolonged systole; 30% ↓HR%CO	32	50% ↓ CO_2-production	32	Extraction ratio of PAH→
Atrial & ventricular dysrythmias 50% ↓ HR % CO	30	Respiratory acidosis 50% ↓ O_2-consumption	30	50% ↓ RBF Autoregulation still intact
Death due to ventricular fibrillation or asystole (Cave! Shivering can mimic ventr. fibr.!)	28		28	RBF & GRF ↓ parallel to ↓ CO
	26	Pulmonary edema Apnea may be present	26	
	24	75% ↓ O_2 - consumption	24	

Central nervous system	°C	Muscles & peripheral nerves	°C	Endocrine system & metabolism
Tiredness		↑↑ Symp. nervous discharge ↑ ALDO		↑↑ NA ↑ corticoids
Silence Apathy	36	↑ tendon reflex Dysarthria Fumbling & stumbling	36	↑T_4 ↑ T_3 TSH → Shivering
Slow cerebration Poor judgement Retrograde amnesia	34	Ataxia	34	Nonshivering thermogenesis?
	32	Muscle rigidity	32	Max. shivering
Consciousness often clouded Stuporous; hallucinations Paradoxical undressing Pupils dilated	30			Insulin inactive Shivering disappears 50% ↓ Basal MBR
No muscle reflex No response to pain No pupillary light reflex		28 25% ↓ Nerve conductivity		28
	26	Physical activity impossible	26	Failing heat conservation Poikilothermia
No corneal reflex	24		24	
Cerebro-vascular auto-regulation disturbed		Local temp.		
	22	12° crit. max. for manual dext. 10° " " " tactile sensitivity	22	
Flat EEG at 19°C		8° complete nervous block		80% ↓ Basal MBR

↑ Increase
→ Stays the same
↓ Decrease

PRIMARY HYPOTHERMIA

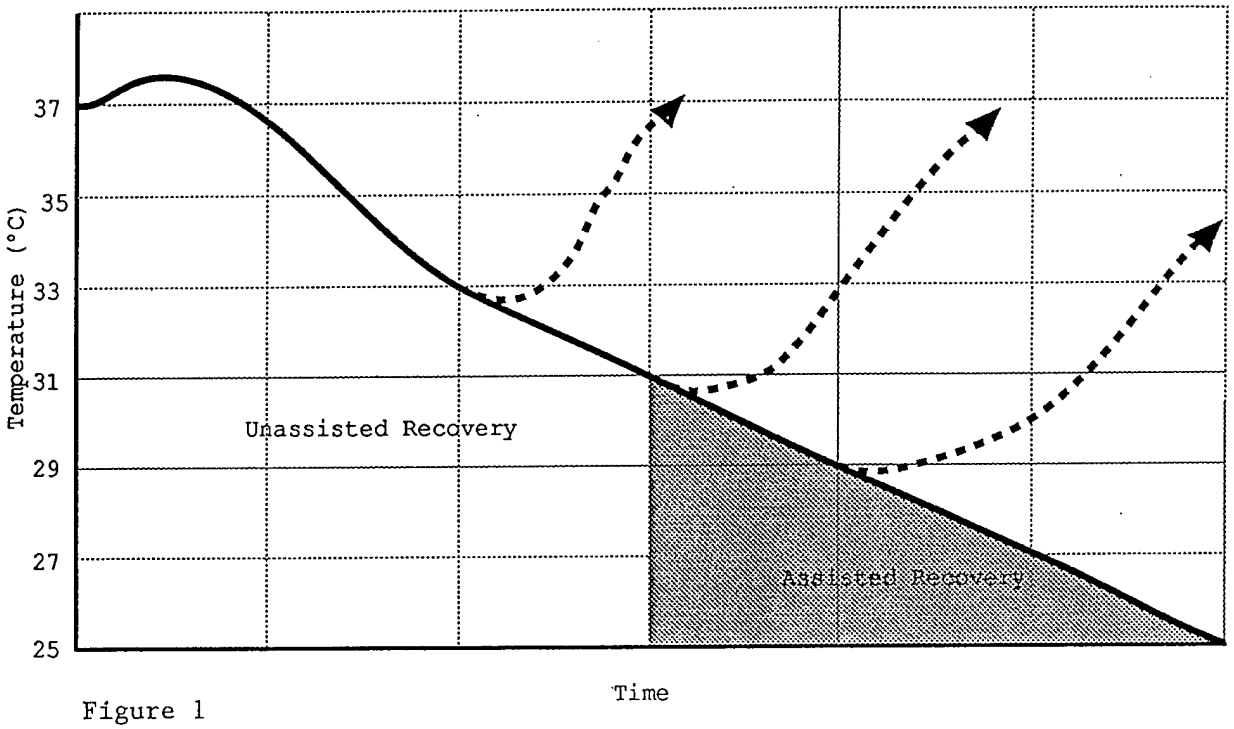

Figure 1

SECONDARY HYPOTHERMIA

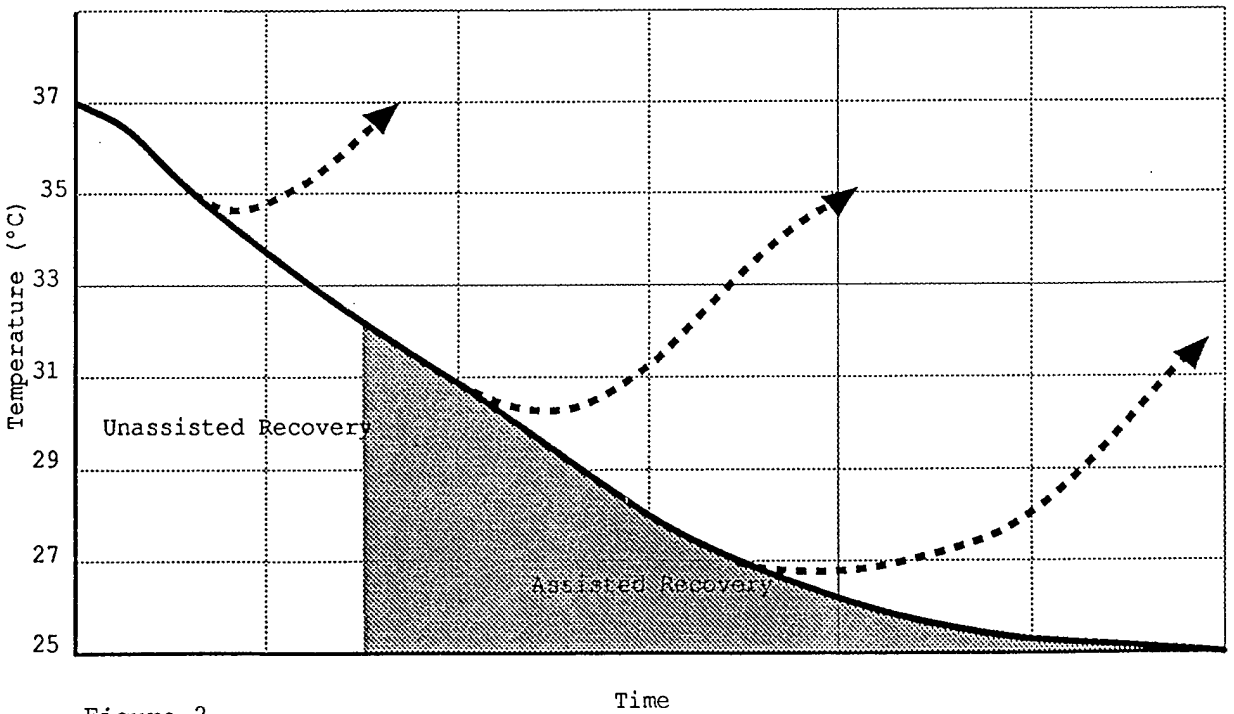

Figure 2

REPORT DOCUMENTATION PAGE

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE & DATE OVERED
	8-9-93	Final

4. TITLE AND SUBTITLE
Limits of Tolerance to Hypothermia

5. FUNDING NUMBERS
Program Element:
Work Unit Number:

ONT Reimbursable

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Report 93-15

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Naval Medical Research and Development Command
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Building 1, Tower 2
Bethesda, MD 20889-5044

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution is unlimited.

12b. DISTRIBUTION CODE
A

13. ABSTRACT *(Maximum 200 words)*

With the advent of sophisticated rewarming techniques, physiologic systems demonstrate great tolerance to hypothermia. Organs can be cooled, and in some cases frozen, leading to a decrease in metabolic demands and then rewarmed with little or no long-term damage.

Not all cases of hypothermia are reversed with rewarming. The major challenge for extending the limits of tolerance to hypothermia is to ascertain the fundamental mechanisms that are unleashed upon rewarming. The microvasculature remains the key site for extending human tolerance to hypothermia. The currently favored hypothesis for frostbit-induced damage is that free radicals are released by reperfusion that subsequently alter vascular tone. Eventually, these changes cause failure of the microcirculation and endothelial cell damage, resulting in thrombosis and necrosis. It is probable that the same cascade of events that occurs in frostbite also occurs during rewarming of the hypothermic patient. Predicting which system will fail upon rewarming is difficult since in many cases the hypothermia is secondary to some underlying pathology.

This review will focus on two aspects of tolerance to the cold: 1) the physiologic effects that occur during hypothermia, and 2) the role various forms of rewarming play in reversing hypothermia.

14. SUBJECT TERMS
Hypothermia

15. NUMBER OF PAGES
55

16. PRICE CODE

17. SECURITY CLASSIFI-CATION OF REPORT	18. SECURITY CLASSIFI-CATION OF THIS PAGE	19. SECURITY CLASSIFI-CATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unclassified